UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/761,913	01/20/2004	Neil Moss	9/216-1-D1	4313

28518 7590 07/03/2007

MICHAEL P. MORRIS
BOEHRINGER INGELHEIM CORPORATION
900 RIDGEBURY RD
P. O. BOX 368
RIDGEFIELD, CT 06877-0368

EXAMINER	
HUYNH, CARLIC K	
ART UNIT	**PAPER NUMBER**
1617	

MAIL DATE	DELIVERY MODE
07/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/761,913	MOSS ET AL.	
	Examiner	Art Unit	
	Carlic K. Huynh	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :20 January 2004 and 5 April 2004.

DETAILED ACTION

Status of the Claims

Claims 1-4 and 6-23 are pending and are considered herewith.

Information Disclosure Statement

The Information Disclosure Statements submitted on January 20, 2004 and April 5, 2004 are acknowledged.

Specification

1. The title of the invention is not descriptive. The present title, "Methods of Treating Cancer" is general. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-4 and 6-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for cytokine mediated cancers including acute myelogenous leukemia, does not reasonably provide enablement for any other cancer or tumor. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors:
(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). ***Nature of the Invention***:

The rejected claim(s) is/are drawn to an invention which pertains to a method of treating cancer comprising administering a compound of formula (I).

(2). ***State of the Prior Art***:

The skilled artisan has recognized various cytokines, namely TNFα, IL-1, IL-8, IL-6, GM-CSF, and INF γ, play a role in the development of various disases including cancer (pages 1-11, Background of the Invention).

(3). ***Relative Skill of Those in the Art***:

The relative skill of those in the art of proinflammatory cytokines is extremely high.

(4). ***Predictability of the Art***:

The treatment of any cancer with the compounds of formula (I) is highly unpredictable. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and that physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Thus, the state of the art is highly unpredictable.

(5). ***Breadth of the Claims***:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass a method of treating cancer comprising administering a compound of formula (I).

(6). ***Direction or Guidance Presented***:

The guidance given by the specification as to the method for treating any cancer with a compound of formula (I) is limited.

The disclosure of the method for inhibiting cytokine production with a compound of formula (I) is adequate (pages 96-97, Assessment of Biological Properties).

(7). ***Working Examples***:

The working examples in the specification show inhibition to various cytokines (pages 96-97, Assessment of Biological Properties). The compounds of formula (I) show inhibition of TNFα in THP cells (page 96, lines 25-26; and page 97, lines 21-22). The compounds of formula (I) also show inhibition of IL-1β, GM-CSF, IL-6, and IL-8 in peripheral blood monocytic cells (page 97, lines 26-29). Thus the compounds of formula (I) are enabled for cytokine mediated cancers including acute myelogenous leukemia.

Furthermore, not all cancers are cytokine mediated. There are many mechanisms by which cells become cancerous such as mutations, chromosomal translocations, abnormalities in the cell cycle, and viral infection. Therefore, the invention may not work with all the various cancers herein claimed.

Thus, the working examples show how to inhibit cytokine production, but do not address any other mechanism by which a cell may become cancerous.

(8). ***Quantity of Experimentation Necessary***:

The specification fails to provide sufficient support of treating any cancer that is not cytokine mediated including acute myelogenous leukemia. As a result, one of skill in the art would be forced to perform an exhaustive search for the embodiments of any cancer other than cytokine mediated cancers including acute myelogenous leukemia having the function recited in the instant claim suitable to practice the claimed invention.

Therefore, in view of the Wands factors, e.g. the predictability of the art, the amount of direction or guidence, and the lack of working examples discussed above, a person of skill in the

art would not be able to fully practice the instant invention without ***undue experimentation***.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-4 and 6-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kapadia et al. (US 6,492,529) in view of Hanna (US 2002/0012665).

Kapadia et al. teach a method of inhibiting cytokine production to treat disorders associated with excess cytokine production comprising administering compounds of formula (I), namely 1-[5-(2-hydroxy-1,1-dimethyl-ethyl)-2-p-tolyl-2H-pyazol-3-yl]-3-[4-(2-morpholin-4-yl-ethoxy)naphthalen-1-yl]-urea and 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(2-morpholin-4-yl-ethoxy)naphthalene-1-yl]-urea (column 18, first compound in table; column 42, lines 61-64; and column 44, lines 40-41).

Kapadia et al. do not teach treatment for cancer, tumors, multiple myeloma, and acute myelogenous leukemia.

Hanna teaches a method for treating hematologic malignancies comprising administrating cytokine antagonists in combination with chemotherapy drugs (abstract and page 3, paragraph [0026]). Hematologic malignancies include acute myelogenous leukemia (page 3, paragraph [0030]). Chemotherapy drugs include alkylating agents (page 10, paragraph [0094]). Hanna

also teaches a method for treating solid non-hematologic (non-lymphoid) tumors, e.g. colorectal or liver cancer (page 1, paragraph [0003]).

To a person of skill in the art at the time of the invention, it would have been obvious to employ the compounds of formula (I) that act as cytokine inhibitors of Kapadia et al. to treat various cancers and tumors including multiple myeloma and acute myelogenous leukemia because the compounds of Hanna are used for treating various cancers and tumors including multiple myeloma and acute myelogenous leukemia and according to Hanna, cytokine antagonists can be used to treat various cancers and tumors including multiple myeloma and acute myelogenous leukemia.

The motivation to combine the compounds of Kapadia et al. to the compounds of Hanna is that the compounds of Hanna are used for treating various cancers and tumors including multiple myeloma and acute myelogenous leukemia.

Regarding genotoxic therapy as recited in instant claim 15, it is also noted that "genotoxic therapy" is well known in the art to be a compound capable of binding DNA and causing a mutation and it is also noted that "alkylating agents" are well known in the art to be compounds that bind to DNA by an alkyl group. Hanna teaches a method for treating hematologic malignancies comprising administrating cytokine antagonists in combination with chemotherapy drugs which include alkylating agents (abstract; page 3, paragraph [0026]); and page 10, paragraph [0094]). Thus it is obvious to one skilled in the art that alkylating agents can be used for genotoxic therapy because they bind to DNA.

Regarding multiple myeloma as recited in instant claims 18 and19, it is noted that "hematologic malignancies" are well known in the art to be a nebulous term encompassing many

malignancies of hemotologic origin including leukemias and multiple myeloma. Since Hanna teaches a method for treating hematologic malignancies, it would be obvious to one skilled in the art that the method of Hanna includes treating multiple myeloma.

Double Patenting

Obviousness-Type

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1, 20, and 22 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 14 and 16 of Cirillo et al. (US 6,319,921), claims 11 and 13 of Cirillo et al. (US 6,329,415), claims 23-25 of Breitfelder et al. (US 6,358,945), claims 12, 14, and 16 of Regan (US 6,372,773), and claim 19 of Cirillo et al. (US 6,825,184) in view of Kapadia et al. (US 6,492,529) and Hanna (US 2002/0012665) as applied to claims 1-4 and 6-23 above.

Kapadia et al. teach a method of inhibiting cytokine production to treat disorders associated with excess cytokine production comprising administering compounds of formula (I) (column 42, lines 61-64).

Hanna teaches a method for treating hematologic malignancies comprising administrating cytokine antagonists in combination with chemotherapy drugs (page 3, paragraph [0026]).

Circillo et al. (US 6,319,921) teach methods of inhibiting cytokine production and treating inflammatory and autoimmune diseases (column 6, lines 23-24; and column 37, lines 24 and 33-34).

Circillo et al. (US 6,329,415) teach methods of inhibiting cytokine production and treating inflammatory and diseases such as adult respiratory distress syndrome (ARDS) (column 6, lines 26-27; column 36, line 39; and column 37, lines 5-6).

Breitfelder et al. teach methods of inhibiting cytokine production and treating cytokine mediated diseases such as adult respiratory distress syndrome (ARDS) (column 6, line 18; column 71, lines 17-18; and column 71, lines 52-53).

Regan teaches methods of inhibiting cytokine production and treating inflammatory and autoimmune diseases such as adult respiratory distress syndrome (ARDS) (column 6, lines 28-29; column 37, lines 17 and 27; and column 37, lines 50-51).

Cirillo et al. (US 6,825,184) teach methods of inhibiting cytokine production and treating cytokine mediated diseases such as adult respiratory distress syndrome (ARDS) (column 7, lines 35-36; and column 48, lines 4 and 20-21).

Thus, it has been established that cancer, tumors, or acute myelogenous leukemia are cytokine mediated and can be treated with compounds of formula (I).

Because the compound of formula (I) is used to treat cytokine mediated disease such as cancer, the method claims of the instant application are not patentably distinct between Cirillo et al. (US 6,319,921), Cirillo et al. (US 6,329,415), Breitfelder et al., Regan, and Cirillo et al. (US 6,825,184).

5. Claims 1, 12-14, 16, and 20-23 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 5-6 of Cirillo et al. (US 6,333,325), claims 3 and 5 of Cirillo et al. (US 6,525,046), and claims 1, 11-13, and 17 of Moss et al. (US 6,825,184) in view of Kapadia et al. (US 6,492,529) and Hanna (US 2002/0012665) as applied to claims 1-4 and 6-23 above.

Kapadia et al. teach a method of inhibiting cytokine production to treat disorders associated with excess cytokine production comprising administering compounds of formula (I) (column 42, lines 61-64).

Hanna teaches a method for treating hematologic malignancies comprising administrating cytokine antagonists in combination with chemotherapy drugs (page 3, paragraph [0026]).

Cirillo et al. (US 6,333,325) teach methods of inhibiting cytokine production and treating cytokine mediated diseases comprising administering compounds of formula (I), namely 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(2-morpholin-4-yl-ethoxy)naphthalene-1-yl]-urea (column 6, lines 16-17; column 36, lines 43-44; and column38, lines 15-16).

Cirillo et al. (US 6,525,046) teach methods of inhibiting cytokine production and treating cytokine mediated diseases comprising administering compounds of formula (I), namely 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(2-morpholin-4-yl-ethoxy)naphthalene-1-yl]-urea (column 7, lines 14-15; column 39, lines 40-41; and column 85, line 6).

Moss et al. (US 6,825,184) teach a method of treating a cytokine mediated disease such as acute and chronic inflammation of the lung caused by inhalation of smoke comprising administering compounds of formula (I), namely 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(2-morpholin-4-yl-ethoxy)naphthalene-1-yl]-urea (column 7, lines 54-56; and column 90, lines 25-26).

Thus, it has been established that cancer, tumors, or acute myelogenous leukemia are cytokine mediated and can be treated with compounds of formula (I).

Because the compound of formula (I) is used to treat cytokine mediated disease such as cancer, the method claims of the instant application are not patentably distinct between Cirillo et al. (US 6,333,325), Cirillo et al. (US 6,525,046), and Moss et al.

Conclusion

6. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carlic K. Huynh whose telephone number is 571-272-5574. The examiner can normally be reached on Monday to Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ckh

S. Wang

SHENGJUN WANG
PRIMARY EXAMINER